

## Functional Connectivity of the Insula in Smokers

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### INTRODUCTION

Nicotine is a highly addictive substance and cigarette smoking is a major cause of death among humans. Nicotine meets all of the DSM-IV criteria for drug dependence, and has been shown to produce tolerance, dependence, and distinct withdrawal syndromes in humans and animals [1]. Nicotine produces profound behavioral effects, but much is still unclear as to its effect on brain function and the underlying neuronal effects. Furthermore, damage to the insula has been shown to disrupt the smoking addiction [2], implicating a brain region or set of regions as the basis for nicotine reception, and addiction. This study seeks to measure changes in connectivity of brain regions associated with the insula as a result of smoking.

### METHODS

Twenty-five known smokers of over a pack a day (20 or more cigarettes) and twenty-five non-smoking control subjects were scanned during a simple finger-tapping task. This fMRI data was processed as resting-state fMRI data to probe low-frequency spontaneous fluctuations underlying task activation [3]. The data was motion corrected, normalized to template space, spatially smoothed, and temporally band pass filtered. Signals from the lateral ventricles, deep white matter, and whole brain mask were regressed out on a voxel by voxel basis as physiological noise. Signal from a seed region in the left insula was used as a regressor of interest to isolate regions functionally correlated [3,4]. Correlation coefficients between seed and all other voxels were then transformed to Fischer Z values for group analyses [4]. Figure 1 shows a significance map of all subject's associated networks with an insula seed.

### RESULTS

The insula seed yields an excellent reproduction of known attention [3] and default mode networks [4,5] across all subjects (fig1). When comparing groups to one another interesting differences appear. The left insula is more functionally connected in smokers to the right supramarginal gyrus, right superior temporal sulcus, and right inferior frontal (fig 2, A, B, and D). Interestingly no significantly greater clusters are seen in the left hemisphere. Also, smokers are correspondingly more negatively correlated than non-smokers in bilateral posterior cingulate.

### DISCUSSION

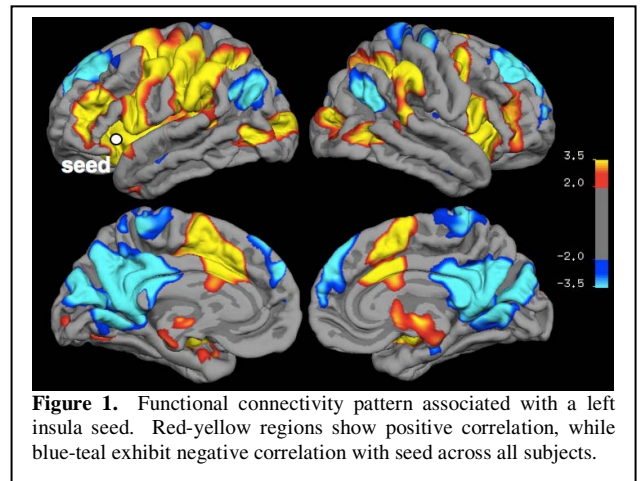
Functional connectivity with the insula and regions described above is fundamentally different in smokers. Interestingly, this analysis shows that the directionality of functional correlations with the insula in smokers remain intact, but the strength of correlation, be it positive or negative, is greater in smokers in regions detailed in figure 2. The posterior cingulate, right supramarginal gyrus, inferior frontal, and superior temporal sulcus, have increased glucose metabolism with the injection of nicotine [6], show increases in task-induced deactivations compared to placebo [7] and all show increased functional connectivity strength with the insula, a region associated with addiction. This information combined, suggests a generalized change in amplitude of bold activation/deactivation and network connectivity caused by nicotine consumption and addiction. The insula is a region that, when damaged, addiction tendencies diminish, and this study shows connections between the insula and regions that activate with nicotine administration.

### ACKNOWLEDGEMENTS

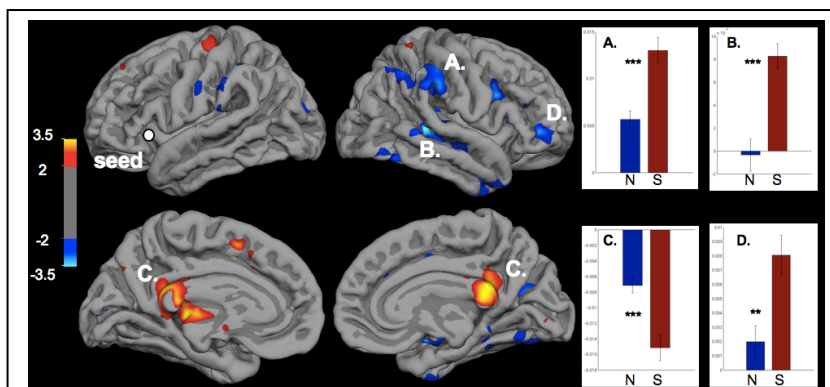
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**Figure 1.** Functional connectivity pattern associated with a left insula seed. Red-yellow regions show positive correlation, while blue-teal exhibit negative correlation with seed across all subjects.



**Figure 2.** Insula functional connectivity changes in smokers. Differences are measured in the right supramarginal gyrus (A.), right superior temporal sulcus (B.), posterior cingulate (C.), and right inferior frontal (D.). Hot colors indicate a positive difference (or less negative) nonsmoker - smoker, while cool colors show a negative difference. Bar charts on right demonstrate directionality of groups, N=nonsmokers (blue) S=smokers (red), \*\*\*  $p < 0.001$ , \*\*  $p < 0.005$ . Y-axis is average correlation Z-value to seed across groups.